Remarks

I. Support for Amendments and Status of the Claims

By the foregoing amendments, the specification is sought to be amended to correct an administrative error in the cross-reference section, as requested by the Examiner. In addition, claims 42-49 and 60-73 are cancelled without prejudice or disclaimer as being drawn to a non-elected restriction group, and claims 50, 53 and 57-59 are sought to be amended. Support for the amendments to claim 50 can be found in the specification at page 10, lines 27-29; at page 15, lines 12-19; at page 16, line 5, to page 17, line 23; throughout the Examples, particularly in Examples 1-3 at pages 20-25; and in claims 22, 34, 37, 40 and 41 as originally filed. The amendment to claim 53 deletes subject matter from this claim, and therefore adds no new matter. The amendments to claims 57 and 58 are sought to enter the SEQ ID NOs for porcine and baboon uricases, respectively, and are supported in the specification at pages 12-13 and 23, and in the sequence listing as filed. The amendment to claim 59 is sought to correct a minor grammatical error.

Hence, these amendments to the specification and claims add no new matter, and their entry and consideration are respectfully requested. Upon entry of the foregoing amendments, claims 50-59 and 74-76 are pending in the application, with claim 50 being the sole independent claim.

II. Summary of the Office Action

In the Office Action, the Examiner has made one objection to the specification, and seven rejections of the claims. Applicants respectfully offer the following remarks to overcome and/or traverse each of these elements of the Office Action.

III. The Objection to the Specification is Accommodated

The Examiner has first objected to the specification, and has required correction, for an allegedly improper cross-reference to a nonprovisional application that had been converted to a provisional application. *See* Paper No. 3 at pages 3-4, section 4. Specifically, the Examiner has stated that "[w]hen a non-provisional application is converted to a provisional application, the serial number of the *converted* non-provisional application should *not* be listed in the continuing data." *Id.* (emphasis in original).

Applicants thank the Examiner for calling this formatting error to their attention. By the foregoing amendments, the specification has been amended such that the continuing data shown in the cross-reference section at page 1 of the application is properly formatted, as required by the Examiner. Hence, it is believed that the objection to the specification has been accommodated.

IV. The Enablement Rejections

In the Office Action at pages 4-7, sections 6 and 7, the Examiner has rejected claims 74-76 under 35 U.S.C. § 112, first paragraph, for allegedly not being enabled by the specification as filed. Applicants respectfully traverse this rejection.

As an initial matter, Applicants note that the Examiner first contends that the present specification "is enabling only for claims limited to a purified porcine uricase." Paper No. 23 at page 4, section 6, line 2. However, this contention is at odds with the subsequent statement by the Examiner that the present specification is "enabling for uricases porcine, baboon, or Chimeric or fusion pig-baboon . . . ." Paper No. 23 at page 5, section 7, lines 2-3. Applicants

respectfully request clarification on this issue, and in any event, respectfully disagree with both contentions and assert that the present specification enables the full scope of uricases recited in the claims as currently presented.

Applicants remind the Examiner that the enablement requirement of 35 U.S.C. § 112, first paragraph, is satisfied if the claimed invention is enabled so that any person skilled in the art can make and use the invention without undue experimentation. *See In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). In order to establish a *prima facie* case of non-enablement, the Examiner has the initial burden to set forth a reasonable basis to question the enablement provided for the claimed invention. *See In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). To satisfy this burden, "it is incumbent upon the Patent Office . . . to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971) (emphasis in original).

The present specification describes a number of representative examples of the claimed genus of uricases, including uricases from various bacteria, molds, plants, and animals (including insects and mammals), as well as for modified uricases, fusion variants, chimeric uricases, and fragments thereof. The specification also provides detailed specifications for the physical and/or structural characteristics of uricase polypeptides (or fragments, variants and derivatives thereof) that would fall within the scope of the present claims. Finally, the nucleic acid and/or polypeptide sequences of a variety of uricases are well-known in the art (*see, e.g.*, specification at pages 1-3) and the use of exemplary uricases

is amply described in the present specification (*see, e.g.*, Figures 1A and 1B (*Candida utilis* uricase); Figures 2A and 2B (porcine uricase); Figures 4A and 4B (*Aspergillus flavus* uricase); and Figures 5A and 5B (*Glycine max*)). Moreover, the present specification clearly teaches residues that are optionally modified to affect the enzymatic activity of a variety of enzymes (including an alignment of the sequences of certain mammalian enzymes; *see, e.g.*, specification at page 23 and in Figure 6). Finally, the present specification clearly teaches exemplary assays that can be used to determine the functionality of a variety of uricases (chimeric, truncated, full-length, etc.), whether or not those uricases are formulated into a pharmaceutical composition (*see, e.g.*, specification at pages 17-19, and particularly in the Examples at pages 20-29). Therefore, one of ordinary skill could readily determine where to modify (*e.g.*, truncate; substitute; delete; fuse; etc.) any uricase based on the information that is available in the present specification, in view of information readily available in the art.

Hence, Applicants submit that the claimed conjugates could be made and used by those of ordinary skill in the art without undue experimentation. Additionally, Applicants respectfully assert a sufficient explanation or sound scientific reasoning as to why the specification would not enable the claimed invention has not been provided. Accordingly, a *prima facie* case of non-enablement has not been established, and under *Marzocchi* and *Wands*, the specification therefore must be taken as enabling the full scope of the invention as claimed.

As the Federal Circuit has held:

> [t]he purpose of [the enablement] provision is to assure that the inventor provides sufficient information about the claimed invention that a person of skill in the field of the invention can make and use it without undue

> experimentation, relying on the patent specification and knowledge in the art.

Scripps Clinic & Research Foundation v. Genentech, Inc., 18 USPQ2d 1001, 1006 (Fed. Cir. 1991). Therefore, the Examiner is respectfully reminded that the proper standard of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosure in the application, coupled with information known in the art, without undue experimentation. *United States v. Telectronics, Inc.,* 8 USPQ2d 1217, 1223 (Fed. Cir. 1988), citing *Hybritech, Inc. v. Monoclonal Antibodies, Inc.,* 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 107 S. Ct. 1606 (1987). It is requested that in reconsidering this rejection, the Examiner also keep in mind that the question of undue experimentation is a matter of degree, and "the key word is 'undue,' not 'experimentation.'" *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), quoting *In re Angstadt*, 190 USPQ 214, 219 (C.C.P.A. 1976). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive. *PPG Indus., Inc. v. Guardian Indus. Corp.,* 37 USPQ2d 1618, 1623 (Fed. Cir. 1996), citing *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984). To demonstrate the efficacy of isolated uricases such as those of the present invention, one of ordinary skill would be prepared to screen candidate uricase compositions for their ability to maintain high uricolytic activity while being substantially reduced in immunogenicity, using *in vitro* and *in vivo* methods that have been well-known in the art for many years and that, in any event, are amply taught in the specification. Indeed, practitioners in the pharmaceutical arts routinely undertake such screening and optimization experimentation without considering it undue. *See Wands*, 8 USPQ2d at 1406. Furthermore, the test of whether an amount of experimentation

is undue is not merely quantitative; a considerable amount of experimentation is permissible, if it is merely routine (*i.e.*, uses methods known to those of ordinary skill in the relevant arts), or if the specification provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. *See PPG Indus.*, 37 USPQ2d at 1623, citing *Ex parte Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. & Inter. 1982). Since the present specification provides significant guidance on how to make and use a variety of uricases and compositions containing such uricases, as well as assays for determining their enzymatic activity and immunogenicity, Applicants respectfully assert that one of ordinary skill could readily make and use the claimed conjugates without the need for undue experimentation.

Moreover, in order to enable a claimed invention a specification need not teach, and preferably omits, information that is well-known to those of ordinary skill in the art. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986); *Lindemann Maschinenfabrik v. American Hoist and Derrick*, 730 F.2d 1452, 1463 (Fed. Cir. 1984); *In re Wands*, 8 USPQ2d 1400, 1402 (Fed. Cir. 1988). In addition, one of ordinary skill in the art is deemed to know not only what is considered well-known, but also where to search for any needed starting materials. *See In re Howarth*, 210 USPQ 689, 692, (C.C.P.A. 1981). As discussed above, the sources, locations, and nucleotide/polypeptide sequences of a variety of uricases are known in the art. In addition, the sources, locations, and nucleotide and/or polypeptide sequences for uricases from bacteria, molds, plants, and animals (including insects and mammals), or fragments, variants and derivatives thereof, are taught in the present specification. Furthermore, as noted above, the present specification also teaches methods of

preparing or obtaining recombinant uricases (or fragments, variants or derivatives thereof), including chimeric uricases, suitable for use in preparing the claimed uricases and compositions. Therefore, in view of the teachings of the present specification and information that is known in the art (which, under *Hybritech*, *Lindemann Maschinenfabrik*, *Wands*, and *Howarth*, need not be taught in, and preferably is omitted from, the present specification), one of ordinary skill would be able to make and use the claimed uricases and compositions with a reasonable expectation of success and without undue experimentation.

Finally, the Examiner contends that claims drawn to pharmaceutical compositions comprising the claimed uricases are not enabled by the present specification. *See* Paper No. 23 at pages 4-5, and at page 7, first full paragraph. Applicants respectfully disagree. The ability of the present uricases to provide uricolytic activity *in vivo*, while not being rapidly cleared from the circulation, is amply shown in the present specification; *see, e.g.*, Example 3 at pages 23-25, and Figures 8-12. In fact, these data have now been published in a peer-reviewed journal (*see* Kelly, S.J., *et al.*, *J. Am. Soc. Nephrol. 12*:1001-1009 (2001), of record as Doc. No. AT13), indicating that those of ordinary skill in the art recognize the therapeutic effectiveness of the claimed uricases. Contrary to the Examiner's contentions at page 7 of the Office Action, the disclosures in these portions of the specification do *not* relate to "a method of administering the composition to an animal for the purpose of obtaining antibodies." The production of anti-uricase antibodies discussed in the specification is an *undesirable* consequence of the introduction of PEG-uricase conjugates into an animal. Indeed, one objective of Applicants' invention is to produce uricases (and compositions or conjugates comprising such uricases) that retain high uricolytic activity while being substantially *reduced*

in immunogenicity. Thus, instead of demonstrating the results of administering the claimed uricases "for the purpose of obtaining antibodies," the data shown and discussed throughout the specification exemplify the ability of the claimed uricases to be used *in vivo* to treat and/or prevent the adverse consequences of hyperuricemia, which depends upon an extension of the circulating half-life of the conjugates (and therefore, a *reduction* in clearance of the conjugates by the immune system). Indeed, the data discussed in Example 3 (and depicted in Figures 8-11) clearly demonstrate the uric acid-lowering effects of the claimed uricases and compositions, and the consequent normalization of pathologic renal structure and function. Hence, there are ample *in vivo* data demonstrating the therapeutic effectiveness of the presently claimed pharmaceutical compositions.

In making these contentions, the Examiner appears to suggest that for the claimed invention to be enabled, Applicants must demonstrate the clinical efficacy of the claimed pharmaceutical compositions (*i.e.*, that the compositions are without obstacles, are safe, and are therapeutically effective). Applicants wish to remind the Examiner, however, that there is no requirement for clinical data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph. In fact, description of *in vitro* and/or animal testing has been held to enable claims to *in vivo* therapeutic compositions and methods of their use:

> In vitro testing, in general, is relatively less complex, less time consuming, and less expensive than in vivo testing. Moreover, in vitro results with respect to the particular pharmacological activity are generally predictive of in vivo test results, i.e., there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are.

Cross v. Iizuka, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *see also In re Brana*, 51 F.3d 1560,

1567-68 (Fed. Cir. 1995) (holding that animal testing results are sufficient to establish whether one skilled in the art would believe that a pharmaceutical compound has an asserted clinical utility for the purposes of compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph). Although the inventions at issue in *Cross* and *Brana* were not the same as that here, these cases are relevant to the present invention because in support of this rejection the Examiner has contended that the present specification lacks specific data regarding use of the claimed uricases and pharmaceutical compositions *in vivo*. To this end, *Cross* and *Brana* have been followed or cited with approval in a number of subsequent cases involving a variety of inventions; *see, e.g., Bigham v. Godtfredsen*, 857 F.2d 1414, 1417 (Fed. Cir. 1988); *Fiers v. Revel*, 984 F.2d 1164, 1169 (Fed. Cir. 1993); *In re Ziegler*, 992 F.2d 1197, 1200-1201 (Fed. Cir. 1993); *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563 (Fed. Cir. 1996); and *Ex parte Bhide*, 42 USPQ2d 1441, 1447 (Bd. Pat. App. Int. 1996). The present specification clearly describes methods for preparation and use of the claimed uricases and pharmaceutical compositions *in vitro* and *in vivo*. Under *Cross* and *Brana*, one of ordinary skill would thus recognize that the animal assays described in the present specification would be "generally predictive of *in vivo* test results," *Cross*, 753 F.2d at 1050, and thus would have a reasonable expectation that the claimed uricases and pharmaceutical compositions could be successfully used in pharmaceutical applications.

In view of the foregoing remarks, Applicants respectfully assert that the specification fully enables the claimed subject matter. Reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph, are respectfully requested.

V. The Written Description Rejection

In the Office Action at pages 7-9, section 8, the Examiner has rejected claims 40-59 and 74-76 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that the claims are drawn to a genus of polypeptide conjugates derived from a number of uricases, but that Applicants have not provided sufficient disclosure to indicate that at the time of filing of the present application, they had possession of conjugates comprising uricases "from any mammalian source." Paper No. 23 at page 8. Applicants respectfully disagree.

Applicants wish to remind the Examiner that "[a]dequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention . . . . the observation of a lack of literal support does not, in and of itself, establish a *prima facie* case for lack of adequate descriptive support under the first paragraph of 35 U.S.C. 112." *Ex parte Parks*, 30 USPQ2d 1234, 1236 (Bd. Pat. App. Int. 1994). Instead, the written description requirement of 35 U.S.C. § 112, first paragraph, is met "if the originally-filed disclosure would have conveyed to one having ordinary skill in the art that an [applicant] had possession of the concept of what is claimed," *id.*, *i.e.*, "[i]f a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification . . . ." *In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir. 1996). An applicant is not required to disclose or provide a working example of every species of a given genus in order to meet the written description requirement of 35 U.S.C. § 112 (*see Parks* and *Alton*), and

subject matter that "might fairly be deduced from the original application" is considered to be described in the application as filed. *Acme Highway Products Corp. v. D.S. Brown Co.*, 431 F.2d 1074, 1080 (6th Cir. 1970) (citations omitted), *cert. denied*, 401 U.S. 956 (1971), *followed by Westphal v. Fawzi*, 666 F.2d 575, 577 (C.C.P.A. 1981). Moreover:

> [a] description of a genus of [polypeptides] may be achieved by means of a recitation of a representative number of [polypeptides], defined by [amino acid] sequence, falling within the scope of the genus . . . .

Regents of Univ. of Calif. v. Eli Lilly & Co., 119 F.3d 1559, 1569 (Fed. Cir. 1997).

As discussed above, the present specification describes a number of representative examples of the claimed genus of uricases, including uricases from various bacteria, molds, plants, and animals (including insects and mammals), as well as for modified uricases, fusion variants, chimeric uricases, and fragments thereof. The specification also provides detailed specifications for the physical and/or structural characteristics of uricase polypeptides (or fragments, variants and derivatives thereof) that would fall within the scope of the present claims. Finally, as also discussed above, the nucleic acid and/or polypeptide sequences of a variety of uricases are well-known in the art (*see, e.g.*, Specification at pages 1-3) and the use of exemplary uricases is amply described in the present specification (*see, e.g.*, Figures 1A and 1B (*Candida utilis* uricase); Figures 2A and 2B (porcine uricase); Figures 4A and 4B (*Aspergillus flavus* uricase); and Figures 5A and 5B (*Glycine max*)). Moreover, the present specification clearly teaches residues that are optionally modified to affect the enzymatic activity of a variety of enzymes (including an alignment of the sequences of certain mammalian enzymes; *see* specification at page 23 and in Figure 6). Therefore, one of ordinary skill would readily understand that the present specification fully describes the

claimed invention, and therefore that Applicants has possession of the claimed invention as of the filing date of the application.

The Examiner also contends that "[c]laims to a specific mutation without reference to a SEQ ID NO. lacks description." Paper No. 23 at page 8, lines 4-5. Applicants respectfully disagree. Applicants note that the only pending claims that recite specific mutations are claims 57 and 58. By the foregoing amendments, these claims have been amended to recite the particular SEQ ID NOs (SEQ ID NO:1 for porcine uricase in claim 57 and SEQ ID NO:2 for baboon liver uricase in claim 58). Hence, this portion of the rejection has been accommodated.

On a related issue, Applicants note that the Examiner contends that the issue of referring to an amino acid residue in one protein by reference to an amino acid position in a related protein may have no meaning. *See* Paper No. 23 at page 8. Applicants respectfully disagree. As those of ordinary skill understand, it is quite common to examine the sequence similarities between closely related proteins (*e.g.*, isozymes; enzymes having the same function but isolated from different animal or plant species; etc.) by aligning their amino acid sequences. In this way, one can readily determine whether, for example, the amino acid at position 301 of porcine uricase is conserved at an amino acid position in another uricase *corresponding* to amino acid 301 (by structural alignment) in porcine uricase. Were this type of alignment and sequence homology characterization not common, the art would not be as replete as it is with sequence alignments of just this sort, examining the relationship between proteins from different species (or even individuals). Indeed, such alignment and analysis is routinely done in the field of molecular evolution, to examine the interrelationships between

molecules (including proteins) based on their sequence similarities. For an example of this type of sequence alignment and analysis, one need only review Figure 1 in Wu *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9412-9416 (1989), cited by the Examiner in the present Office Action (Document "V" on the Form PTO-892 attached to Paper No. 23) and relied upon by the Examiner in a rejection addressed below. In this Figure, Wu *et al.*, make the very point made above -- that although there may be differences in the individual amino acids between uricases from different animal species, an alignment of the sequences of these proteins provides a frame of reference such that one of ordinary skill can readily determine what amino acid in murine or porcine uricase corresponds to a given amino acid position in the baboon uricase sequence. Wu *et al.* then go on to draw detailed conclusions regarding the molecular evolution of uricase proteins in different species based at least in part on these sequence alignments (*see, e.g.*, Wu *et al.* at pages 9414-9416).

Moreover, the Examiner's concerns relating to the amino acid sequence of rat liver uricase (Paper No. 23, page 8) are unfounded. The Examiner contends that rat liver uricase only has 289 amino acids, and therefore that modifications at positions 291 or 301 would be undefined in this molecule. However, in support of this statement, the Examiner has cited a reference (Motojima *et al.*, *J. Biol. Chem 263*:16677 (1988)) that has an incorrect, truncated sequence for rat liver uricase. The Motojima reference is reference 13 cited in the Wu *et al.* reference referred to above (and cited by, and relied upon, by the Examiner in the present Office Action). Wu *et al.* state that the sequence for rat liver uricase reported by Motojima *et al.* is shorter than the actual sequence for rat liver uricase, probably due to "sequencing errors that result in frame shifts and shortened open reading frames." Wu *et al.* at page 9415,

col. 2, paragraph 1. In fact, the complete amino acid sequence for rat liver uricase is known to be 303 amino acids in length (*see, e.g.*, Wang *et al.*, *Gene 97*:223-229 (1991) (showing that the rat liver uricase sequence has 303 residues including N-terminal Met, and ending in the C-terminal peroxisome targeting signal sequence "LPSRL"); Alvares *et al.*, *Biochem. Biophys. Res. Commun. 158*:991-995 (1989) (showing that the nucleotide sequence for rat liver uricase contains an open reading frame coding for 303 amino acid residues); and the amino acid sequence for rat liver uricase deposited with the Protein Database at NCBI/NIH (showing an amino acid sequence of 303 residues); these documents are cited in the Supplemental Information Disclosure Statement filed herewith as Doc. Nos. AR19, AS19 (abstract only), and AT19, respectively). Hence, one of ordinary skill could readily determine the corresponding amino acid in other uricases by reference to a given amino acid position in, for example, baboon or porcine uricase.

Therefore, the "representative number" standard under *Eli Lilly*, upon which the Examiner has apparently based this rejection, is clearly met by the present specification -- a large variety of uricases (and fragments, variants and derivatives thereof) from many different species are taught by the present specification. Hence, Applicants respectfully assert that the present specification provides sufficient written description to convey to one of ordinary skill that Applicants had possession of the full scope of the claimed invention upon filing of the application.

In view of the foregoing remarks, Applicants respectfully assert that the specification as originally filed fully describes claims 50-59 and 74-76 as currently presented. Reconsideration and withdrawal of this rejection therefore are respectfully requested.

VI. The Rejections Under 35 U.S.C. § 112, Second Paragraph

In the Office Action at pages 9-10 (sections 9 and 10), the Examiner has rejected claims 50-59 and 74-76 under 35 U.S.C. § 112, second paragraph, for alleged indefiniteness. Applicants respectfully traverse this rejection.

A. The Rejection of Claims 50 and 53

In making this rejection, the Examiner has first rejected claim 50 for reciting a tetrameric uricase that is "substantially free" of "uricase aggregates." *See* Paper No. 23 at page 9, section 9, second paragraph. With respect to the recitation of "substantially free," claim 50 has been amended such that this phrase has been deleted. Hence, this portion of the rejection has been overcome by the foregoing amendments; reconsideration and withdrawal are respectfully requested. Applicants respectfully disagree, however, that the recitation of "uricase aggregates" in claim 50 renders this claim indefinite. Claim 50 as currently presented recites uricases "containing no more than about 10% non-tetrameric uricase aggregates." Hence, one of ordinary skill would readily understand that the uricase aggregates recited in claim 50 are *non-tetrameric* aggregates, and that the uricase of claim 50 contains no more than about 10% of such aggregates. As the present specification clearly teaches at pages 16-17, and in Example 1 at pages 20-21, whether or not a given uricase preparation contains more than about 10% non-tetrameric uricase aggregates can be readily determined by one of ordinary skill using a variety of routine methods, including, *e.g.*, chromatographic methods such as those disclosed in the specification and that are known in the art. As the Board has held:

> [35 U.S.C. § 112, second paragraph] merely requires that the claims set forth and circumscribe a particular area with a reasonable degree of precision and particularity. The definiteness of the claim language employed must not be analyzed in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one having ordinary skill in the pertinent art.

Ex parte Moelands, 3 USPQ2d 1474, 1476 (Bd. Pat. App. Int. 1987) (citing *In re Moore*, 439 F.2d 1232 (CCPA 1971). Since the levels of non-tetrameric uricase aggregates present in a given uricase are easily determined using routine methods that are taught in the specification and that are known in the art, one of ordinary skill could easily determine the scope of the phrase "non-tetrameric uricase aggregates" as recited by the present claims. Claim 50 thus comports with the requirements of 35 U.S.C. § 112, second paragraph, as interpreted under *Moelands* and *Moore*, and therefore is not indefinite; reconsideration and withdrawal of this portion of the rejection therefore are respectfully requested.

The Examiner also contends that claim 53 is indefinite for reciting "substantially the sequence of porcine . . . .," and has suggested that the phrase "substantially" be deleted. Paper No. 23 at page 9, section 9, second and third paragraphs. Applicants respectfully disagree, and assert that one of ordinary skill could readily determine the metes and bounds of a uricase that has substantially the sequence of a given reference uricase. However, to expedite prosecution and allowance of the present application, and not in acquiescence to this rejection, claim 53 has been amended to delete the word "substantially," as suggested by the Examiner. Hence, this portion of the rejection has been accommodated; reconsideration and withdrawal are respectfully requested.

B. The Rejection of Claims 57-58

The Examiner has next rejected claims 57 and 58 as allegedly being indefinite for reciting mutational modifications of specific amino acid residues without reference to a SEQ ID NO. *See* Paper No. 23 at pages 9-10, section 10. By the foregoing amendments, claims 57 and 58 have been amended to recite the appropriate SEQ ID NOs. Accordingly, this portion of the rejection has been accommodated; reconsideration and withdrawal are respectfully requested.

C. Summary

In view of the foregoing remarks, Applicants respectfully assert that claims 50-59 and 74-76 particularly point out and distinctly claim the subject matter regarded by Applicants as the invention. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, therefore are respectfully requested.

VII. The Rejection Under 35 U.S.C. § 102(b) Over Chen I

In the Office Action at page 10, section 11, the Examiner has rejected claims 50-53 under 35 U.S.C. § 102(b) as allegedly being anticipated by Chen *et al.*, *Biochim. Biophys. Acta 660*:293-298 (1981) (of record as Doc. No. AS11; hereinafter "Chen I"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner contends that Chen I discloses all of the elements of the claimed invention. Applicants respectfully disagree. Specifically, claim 50 (and thus the remaining claims, all of which depend directly or ultimately therefrom) is drawn

to an isolated tetrameric mammalian uricase "containing no more than about 10% non-tetrameric uricase aggregates." This element of claim 50 is not expressly or inherently disclosed in Chen I.

As discussed in the present specification at page 16, lines 5-16, purified preparations of natural and recombinant uricase usually contain a mixture of aggregates of the enzyme, in addition to the tetrameric form. The estimated percentage of the non-tetrameric form of the enzyme present in typical preparations varies from more than 10% to about 80%. *See id.* Hence, without specifically purifying the uricase to remove such non-tetrameric aggregates, uricase preparations such as those described in Chen I will contain substantial quantities (*i.e.*, more than about 10%) of the non-tetrameric form of the enzyme. *See id.* Thus, as one of ordinary skill would readily appreciate, the methods disclosed in Chen I would not result in the production of isolated tetrameric mammalian uricases containing no more than about 10% non-tetrameric uricase aggregates.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984). In addition, a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient enabling detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("To anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). As noted above, Chen I does not

expressly or inherently disclose the production of a uricase that has been purified such that it contains no more than 10% non-tetrameric uricase aggregates. Thus, this reference cannot and does not anticipate the claimed invention.

In view of the foregoing remarks, Applicants respectfully assert that Chen I does not anticipate claims 50-53 as currently presented. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Chen I therefore are respectfully requested.

VIII. The Rejection Under 35 U.S.C. § 102(b) Over Chen II

In the Office Action at page 10, section 12, the Examiner has rejected claims 50-53 under 35 U.S.C. § 102(b) as allegedly being anticipated by Chen *et al.*, *Science 239*:1288-1291 (1988) (of record as Doc. No. AT14; hereinafter "Chen II"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner essentially reiterates the contentions made above regarding Chen I, by stating that Chen II discloses the production of porcine uricase "which is tetrameric and is substantially pure or free of uricase aggregates." Paper No. 23 at page 10, section 12. Applicants respectfully disagree. As noted above, the present specification teaches that purified preparations of natural and recombinant uricases usually contain a mixture of non-tetrameric aggregates of the enzyme, which typically varies from more than 10% to about 80%. Hence, without specifically purifying the uricase to remove such non-tetrameric aggregates, uricase preparations such as those described in Chen II will contain substantial quantities (*i.e.*, more than about 10%) of the non-tetrameric form of the enzyme. Chen II does not indicate that the uricases disclosed therein were purified in such

a way as to reduce the level of non-tetrameric uricase to no more than about 10%. In fact, the Examiner has pointed to no express disclosure in Chen II that would support the Examiner's statement that the uricase disclosed therein "is tetrameric and is substantially pure or free of uricase aggregates." Absent this express disclosure, or the presentation of sound scientific reasoning indicating that Chen II inherently discloses uricases having the characteristics recited in claim 50, this reference cannot support a rejection under 35 U.S.C. § 102(b). *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984).

In view of the foregoing remarks, Applicants respectfully assert that Chen II does not anticipate claims 50-53 as currently presented. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Chen II therefore are respectfully requested.

IX. The Rejection Under 35 U.S.C. § 102(b) Over Sigma

In the Office Action at page 10, section 13, the Examiner has rejected claims 50-53 under 35 U.S.C. § 102(b) as allegedly being anticipated by any of a number of specific compounds (Product Nos. U 3250, 292-8, U 3500, U 9375 or U 3377) disclosed in the Sigma catalogue, page 1002 (1993) (Doc. No. "W" cited on the Form PTO-892 attached to Paper No. 23; hereinafter "Sigma"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner essentially reiterates the contentions made above regarding Chen I and Chen II, by stating that Sigma represents the commercial availability of uricases that "inherently are tetrameric and is [sic] substantially pure or free of uricase aggregates." Paper No. 23 at page 10, section 13. Applicants respectfully disagree.

As noted above, the present specification teaches that purified preparations of natural and recombinant uricases usually contain a mixture of non-tetrameric aggregates of the enzyme, which typically varies from more than 10% to about 80%. Hence, without specifically purifying the uricase to remove such non-tetrameric aggregates, uricase preparations such as those available from Sigma will contain substantial quantities (*i.e.*, more than about 10%) of the non-tetrameric form of the enzyme. There is no indication that the uricases listed in the Sigma catalogue referenced by the Examiner were purified in such a way as to reduce the level of non-tetrameric uricase to no more than about 10%. In fact, the Examiner has pointed to no express disclosure in Sigma that would support a conclusion that the Sigma uricases are tetrameric and substantially pure or free of uricase aggregates.

Recognizing that the Sigma disclosure fails to expressly anticipate the presently claimed invention, the Examiner instead contends that Sigma *inherently* discloses the invention. *See* Paper No. 23 at page 10, section 13. Applicants respectfully disagree with this contention, and wish to remind the Examiner that "[i]n order for a disclosure to be inherent . . . the missing descriptive matter must necessarily be present in the [cited reference] such that one skilled in the art would recognize such a disclosure." *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1159 (Fed. Cir. 1998). Moreover, to rely on an inherency argument, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PTO Bd. Pat. App. Int. 1990) (emphasis in original). That is, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient."

Continental Can Co. USA, Inc. v. Monsanto Co., 948 F.2d 1264, 1269 (Fed. Cir. 1991). In the present case, the Examiner has pointed to no disclosure in Sigma that is "necessarily present" such that it would be recognized as by one of ordinary skill as disclosing uricases that contain no more than about 10% non-tetrameric uricase aggregates (thus, the *Tronzo* standard is not met by Sigma). Moreover, as noted above, Sigma contains no express disclosure that the uricases listed therein have been purified in such a way as to reduce the level of non-tetrameric uricase aggregates to no more than 10%. The Examiner has pointed to no disclosure in Sigma, and has provided no sound scientific reasoning, to support the notion that this missing disclosure in Sigma "*necessarily* flows" from what *is* disclosed in Sigma (thus, the *Levy* standard is not met by Sigma). Finally, one of ordinary skill, reading the simple listings of uricases in the excerpts from the Sigma catalogue cited by the Examiner, could find no disclosure indicating that it was even possible, let alone probable, that the Sigma uricases would have the properties recited by claim 50 (thus, the *Continental Can* standard is not met by Sigma). Hence, the Examiner's attempted reliance upon inherent anticipation in the present case is factually and legally unfounded.

Accordingly, Sigma does not expressly or inherently disclose the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b).

In view of the foregoing remarks, Applicants respectfully assert that Sigma does not anticipate claims 50-53 as currently presented. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Sigma therefore are respectfully requested.

X. The Rejection Under 35 U.S.C. § 102(b) Over Wu

In the Office Action at page 11, section 14, the Examiner has rejected claims 50-53 under 35 U.S.C. § 102(b) as allegedly being anticipated by Wu *et al.*, *Proc. Natl. Acad. Sci. USA 86*:9412-9416 (1989) (of record as Doc. No. 41 in Applicants' Information Disclosure Statement filed on September 17, 2001; hereinafter "Wu"). Applicants respectfully traverse this rejection.

In making this rejection, the Examiner essentially reiterates the contentions made above regarding Chen I, Chen II and Sigma, stating that Wu discloses the production of urate oxidase from baboon, mouse and pig and that "[t]he sequences are as pure as any protein can get and being free of aggregates anticipates the claims." Paper No. 23 at page 11, section 14. Applicants respectfully disagree. As discussed in detail above, simply because a uricase has been produced recombinantly and "purified" does not mean that that uricase is "free of aggregates" to any particular level, let alone that it contains not more than 10% non-tetrameric uricase aggregates. Hence, without specifically purifying the uricase to remove such non-tetrameric aggregates, the uricase preparations disclosed in Wu will contain substantial quantities (*i.e.*, more than about 10%) of the non-tetrameric form of the enzyme. There is no express disclosure in Wu that the uricases disclosed therein were purified in such a way as to reduce the level of non-tetrameric uricase to no more than about 10%. In fact, the Examiner has pointed to no express disclosure in Wu that would support the statement that the Wu uricases are "free of aggregates."

If instead the Examiner is basing this rejection upon the possible inherent disclosure of the claimed uricases in Wu, Applicants respectfully disagree with this approach. As noted

above, to rely on an inherency argument, "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic *necessarily* flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (PTO Bd. Pat. App. Int. 1990) (emphasis in original). This burden has not been met in the present case, since the Examiner has pointed to no disclosure in Wu, nor any sound scientific reasoning, that uricases containing no more than about 10% non-tetrameric uricase aggregates "necessarily flow" from the disclosure in Wu. Indeed, as discussed in detail above, the present specification clearly shows that by preparing uricases according to the methods of Wu, but without undertaking the additional isolation procedures used to produce the presently claimed uricases, one of ordinary skill at best would succeed in preparing uricases that contain *more* than about 10% non-tetrameric uricase aggregates. Thus, any reliance upon inherent anticipation by Wu is factually and legally unfounded.

Accordingly, Wu does not expressly or inherently disclose the presently claimed invention. Hence, under *Kalman*, this reference cannot support a rejection under 35 U.S.C. § 102(b).

In view of the foregoing remarks, Applicants respectfully assert that Wu does not anticipate claims 50-53 as currently presented. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 102(b) over Wu therefore are respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider and withdraw all of the outstanding objections and rejections, and allow all pending claims.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt consideration of the foregoing amendments and remarks, and allowance of all pending claims, are earnestly solicited.

Respectfully submitted,

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